REMARKS/ARGUMENTS

I. Status of the Claims

Claims 1-7, 10-13, and 15 are pending. Claims 8, 9, 14, 21, 22, 25, 37, 38, 40, 49, 52, 71, 72, 74, 85, 86 and 88 have been canceled. Claims 16-20, 23, 24-36, 39, 41-48, 50, 51, 53-70, 73, 75-84, 87, and 89-93 are withdrawn as drawn to a non-elected invention.

II. The Amendments

The amendments herein present no new matter.

The amendments to the specification reword embedded hyperlinks to avoid active hyperlinks and delete a repeated word.

The amendment to claim 1 recites that the ligands are antibodies or peptides. That the ligands can be antibodies and peptides is supported throughout the specification, including page 18, lines 17-18. The amendment to claim 11 adds a comma to separate the recitation that the ligand binds pIgR from the recitation regarding the presence of a biologically active component. The amendment is supported throughout the specification, including page 14, lines 19-25.

III. The Office Action

The Office Action dated September 23, 2003 (the "Action") objects to the specification and rejects the pending claims on several grounds. Applicants amend in part and traverse all the rejections, as set forth in more detail below.

A. Objection to the Specification

The Action objects to the specification for containing an embedded hyperlink and requires its removal.

Applicants have reworded two hyperlinks in the specification so that they will not form active hyperlinks when placed on the PTO website. The amendments are believed to obviate the rejection.

B. Rejection of the Claims under 35 U.S.C. § 112, Second Paragraph

The Action rejects claims 1-7, 10-13, and 15 under 35 U.S.C. § 112, second paragraph as allegedly indefinite. According to the Action, claim 1 is indefinite and ambiguous for reciting "binds to the most abundant form of SC present in the organ" and "does not bind to the stalk under physiological conditions." Action, at page 3. The Action states that the "characteristics and metes and bounds" of these terms are "unclear and indefinite. *Id.* Applicants traverse. As explained in more detail below, the rejection does not apply the standard required by the MPEP. Further, a review of the claims under the correct standard shows that the claims meet that standard. The rejection should therefore be reconsidered and withdrawn.

1. The MPEP's standard for judging definiteness.

The MPEP provides a specific standard which the examining corps is to use in judging definiteness. Applicants respectfully call the Examiner's attention to MPEP § 2173.02 (8th Ed., Feb. 2003 revision) (all citations herein are to this revision of the MPEP). Section 2173.02 instructs that claims should be allowed which

> define the patentable subject matter with a reasonable degree of particularity and distinctness. Some latitude in the manner of expression and the aptness of terms should be permitted even if the claim language is not as precise as the Examiner might wish.

MPEP at page 2100-198 to page 2100-199, bridging paragraph (emphasis in original). Further, § 2173.02 gives the Examining Corps the following instructions:

> The essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum but in light of:
>
> (A) The content of the particular application disclosure;
>
> (B) The teachings of the prior art; and

> (C) The claim interpretation that would be given by one possessing the ordinary level skill in the pertinent art at the time the invention was made.
>
> In reviewing a claim for compliance with 35 U.S.C. § 112, second paragraph, the examiner must consider the claim as a whole to determine whether the claim apprises one of ordinary skill in the art as of its scope and, therefore, serves the notice function required by 35 U.S.C. 112 second paragraph by providing clear warning to others as to what constitutes infringement of the patent.

MPEP §2173.02, at page 2100-199 (emphasis added).

2. The MPEP standard has been met with regard to the terms at issue

(i) The MPEP's analysis has not been followed in finding the claims indefinite

Applicants respectfully observe that the rejection of the claims as indefinite is not based on the analysis required by the MPEP. The **entirety** of the rejection reads as follows:

> Claim 1 is indefinite and ambiguous in the recitation of "binds to most abundant form of SC present in the organ" and "does not [bind] to the stalk under physiological conditions." The characteristics and metes and bounds of "most abundant form of SC present in the organ" and "physiological conditions" are unclear and indefinite."

Action, at page 3.

This statement does not reflect, and does not contain, the required analysis of the teachings of the specification, the teachings of the prior art, or the interpretation that would be given the claims by a person of ordinary skill in the art. The rejection is therefore not based on the analysis required by the MPEP before a rejection for indefiniteness can be made. As shown below, following the standard set forth in the MPEP results in the conclusion that the claims define the invention with the reasonable degree of clarity and particularity required.

(ii) Properly analyzed, the term "physiological conditions" meets the standard

Applicants turn first to the Action's rejection of the term "physiological conditions." The Action provides no analysis or reasoning why a person of ordinary skill in the art, typically in this art a Ph.D. or M.D. level scientist, would be unable to determine what constitutes a "physiological condition." In particular, the Action does not indicate the interpretation that would be given to the term by a person of ordinary skill or why that interpretation would be deficient in giving notice as to what would constitute infringement of the patent. The Examiner's attention is respectfully directed to the specific definition of the term "physiological conditions" in the specification at page 26, lines 27-33:

> "The term 'physiological conditions' is used herein in two meanings. With reference to culturing cells and the like, it means an extracellular milieu having conditions (e.g., temperature, pH, and osmolarity) which allows for the sustenance or growth of a cell of interest. With reference to [the] species of secretory component (SC) which is most abundant under such conditions, "physiological conditions" refers to the conditions normally present in the organ of interest or tissue of interest, such a the lumen of the small or large intestine."

As noted, under the MPEP, whether or not the claims set forth the invention with reasonable particularity is judged in light of the teachings of the specification, the prior art and the manner in which the claims would be interpreted by one of ordinary skill. In the present instance, the specification contains a specific definition of the objected to term. The Action does not acknowledge the existence of the definition, nor indicate why a Ph.D. or M.D. level scientist would be confused by the conditions (such as pH, temperature and osmolarity) normally present in any particular organ of the body. Applicants surmise that the Action inadvertently overlooked the presence of this definition in the specification. Applicants request that the rejection be reconsidered, and withdrawn, in light both of the explicit definition provided by the specification and the standard set forth by the MPEP.

(iii) Applying the MPEP's standard, the terms "most abundant form of the SC" and "does not bind to the stalk" are not indefinite

Like the term "physiological conditions," the terms "most abundant form of the SC" and "does not bind to the stalk" are rejected on the basis of a conclusion, without acknowledgement or analysis of the specification's teachings, the prior art, or the interpretation that the specification's teachings would be given by a person of skill in the art.

In this regard, the rejection does not consider:

(1) the detailed teachings in the specification for determining the major species of the SC present in an organ or tissue of interest, as set forth in the specification at page 42, line 8, to page 44, line 5;

(2) the detailed teachings in the specification for identifying the stalk of the polymeric immunoglobulin receptor ("pIgR"), as set forth in the specification at page 35, line 25, to page 36, line 14; and

(3) the detailed assays set forth at length in the Examples in the specification by which the practitioner can determine whether any particular ligand binds or does not bind to the major species of SC present in an organ after proteolytic cleavage of pIgR and does or does not bind to the stalk remaining at the cell surface, as set forth in the specification at Example 7, page 66, line 25, to page 72, line 25.

The Action asserts that the metes and bounds of the terms "most abundant form of the SC" and "does not bind to the stalk" are ambiguous. But, Applicants respectfully note this is merely a conclusion, not the analysis required by the MPEP. Any analysis would have to take into account the functional recitation in the claims, the detailed teachings in the specification noted above, the assays taught in the Examples, and the interpretation that would be given the terms by the person of ordinary skill. Applicants respectfully submit that, analyzed in light of these factors, the terms "most abundant form of the SC" and "does not bind to the stalk" have the requisite degree of clarity or a degree of particularity. As noted quoted above, MPEP §2173.02 requires only a reasonable degree of clarity and particularity.

Applicants submit that the detailed teachings set forth in the specification, coupled with the assays set forth in the Examples, permit the practitioner to readily determine

whether any particular ligand falls within the scope of the claims. The Action contains no analysis demonstrating that the teachings set forth in the specification are insufficient or would not be capable of appropriate interpretation by persons of skill in the art. And, even if there was some ambiguity, which Applicants do not concede, MPEP §2173.02 instructs the examining corps that "[s]ome latitude in the manner of expression and the aptness of terms should be permitted even if the claim language is not as precise as the Examiner might wish."

In short, there is no evidence that there would be any confusion or lack of notice that would, in the words of the MPEP, fail to provide "clear warning to others as to what constitutes infringement of the patent." To the contrary, Applicants submit that, given the detailed teachings of the specification, persons of skill are given "clear warning to others as to what constitutes infringement of the patent," and the purposes of the requirements of §112, second paragraph have been met. The rejection should be reconsidered in light of the detailed teachings set forth in the specification and the standard set forth in the MPEP and, upon reconsideration, should be withdrawn.

C. Rejection of the Claims under 35 U.S.C. § 112, First Paragraph

1. The rejection does not present a *prima facie* case of lack of enablement

Claims 1-4, 10-13, and 15 are rejected under 35 U.S.C. § 112, first paragraph as not enabled "for *any* ligand that binds to *any* region of pIgR or *any* ligand comprising a binding component for binding to *any* region of pIgR and *any* biologically active component." Action at pages 3-4, bridging paragraph (emphasis in original). According to the Action, there is insufficient guidance to make such ligands, and Applicant has not provided sufficient biochemical information (such as structural characteristics or amino acid composition) to make such agents. According to the Action, the techniques required to use a ligand which is an antibody is different than that required to use non-antibody proteins and peptides in binding assays. Action, at page 4, bottom paragraph. Applicants amend in part and traverse.

As a threshold matter, Applicants note that the rejection fails to set forth a *prima facie* case that the claims are not enabled. The Examiner is respectfully reminded that the Examiner "has the initial burden to establish a reasonable basis to question the enablement

provided for the claimed invention." MPEP § 2164.04. The MPEP further reminds the examining corps that, under the court's decision in *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971), the Patent Office has the burden to state not only "*why* it doubts the truth or accuracy of any statement in a supporting disclosure," but also "to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." MPEP § 2164.04, *quoting In re Marzocchi, supra*, at page 370 (emphasis in original).

Applicants respectfully submit that the rejection under § 112, first paragraph fails to meet this standard. The Action does not present reasoning or evidence inconsistent with the contested statements. Except for one statement, discussed below, it simply offers conclusory statements that the specification fails to provide sufficient guidance. But, unsupported assertions are not sufficient to meet the burden placed upon the Office. If they were, *Marzocchi* and MPEP § 2164.04 would be meaningless, since in every case an examiner could meet his or her burden simply by making an unsupported assertion of unpredictability. In the words of *Marzocchi*, "there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure" if the Office could defeat the specification by such a simple expedient.

The Action does offer one statement that appears to be based on a reference. The Action states:

The techniques required to use a ligand which is an antibody differ from those required to use other non-antibody proteins and peptides, nucleic acids in binding assays. For instance, Ferkol et al (IDS) teach that while antibody may be used as the ligand for receptor mediated gene transfer, the natural ligands may be unstable.

Action, at page 4.

Applicants are uncertain which of the two Ferkol references cited in the IDS the Action references, exactly what the Action's statement is intended to mean, the nature of the instability of the natural ligands (to pIgR?) is, or what the relationship the Action considers there to be between the alleged instability of the "natural ligands" of one of the Ferkol references and

the ligands of the claims under examination. Should the rejection be maintained in any future office action, Applicants respectfully request that the Examiner clarify this contention so that they may respond more completely. On the basis of the rejection as articulated in the present Action, however, Applicants respectfully submit that the Action fails, in the words of the MPEP § 2164.04 "to back up [its] assertions with acceptable evidence or reasoning which is inconsistent with the contested statement."

Accordingly, Applicants respectfully maintain that the rejection must be reconsidered and either supported with evidence or reasoning, or withdrawn.

(2) Rejection as not enabled for binding to *any* region of pIgR

As set forth in the preceding section, Applicants respectfully maintain that the Action fails to meet the requirements set forth in the MPEP for presenting a rejection for alleged lack of enablement. As also noted above, the rejection should be reconsidered and withdrawn on this basis alone. For the sake of good order, however, Applicants turn now to a consideration of the various statements set forth in the rejection.

The Action contends that the specification provides insufficient guidance and direction on how to make ligands that bind to "*any* region of pIgR". Action at, e.g., page 4 (emphasis in original). Applicants observe that the rejection is founded on a false premise. The claims under examination do not recite or require ligands that bind "*any* region of pIgR". While claim 1 begins by reciting "[a] ligand that binds specifically to a region of a polymeric immunoglobulin receptor," it continues by reciting that the ligand "does not substantially bind to the most abundant form of [secretory component] present in the organ of interest and provided further that the ligand does not bind substantially to the stalk." Thus, claim 1 does not recite ligands that bind to *any* portion of pIgR, as the Action asserts, but rather ligands that bind to a region of pIgR positioned between the most abundant form of the SC and the stalk -- what the specification terms the "B region."

Thus, the Action's reading ignores two functional recitations regarding where the ligands of the invention bind, which define the ligands as binding to the B region. Since the other claims under examination depend from claim 1 and, therefore share the same recitations,

they too refer to ligands that bind the B region. Accordingly, the enablement rejection of claims 1-4, 10-13, and 15 is founded on an erroneous reading of those claims, and should be reconsidered, and withdrawn on this basis alone.

The rejection would be incorrect in any event because persons of skill were enabled to find ligands for binding to any portion of pIgR prior to the filing of the present specification. The sequence of pIgR was known prior to the filing of the present application and is set forth in Figure 1. Standard techniques were available in the art for identifying peptides, antibodies and other molecules that bind to any particular target of interest. See, the Declaration of Dr. Jacqueline M. Glynn under 37 C.F.R. § 1.132 attached hereto (hereafter, the "Declaration"), at paragraph 6. These techniques, such as phage display, permitted rapidly screening libraries of peptides for peptides capable of binding to any particular portion of pIgR. Thus, while any particular ligand might be novel and inventive, the specification enabled persons of skill to make and use antibodies and peptides that bind to the B region. Applicants respectfully note that, of course, there was no recognition in the art that it would be advantageous to generate ligands to the B region prior to the teachings of the present specification.

(3) Rejection regarding ligand comprising a ligand binding to any region of pIgR and any biologically active component

The rejection under §112, first paragraph, also rejects claims 1-4, 10-13, and 15 under §112, as not enabled for "*any* ligand comprising a binding component for binding to *any* region of [pIgR] and *any* biologically active component." Action at, e.g., page 4, top two lines (emphasis in original). Thus, this portion of the rejection appears to contend that the ligand binds to any biologically active component. Applicants amend in part and traverse.

(a) This rejection applies only to claims 11-15

For the sake of good order, Applicants note that this portion of the rejection can apply only to claims 11-15, since they are the only claims under examination that contain a recitation that the ligand further comprises a binding component and a biologically active component. Thus, this portion of the enablement rejection is not applicable to claims 1-4 or 10.

(b) The rejection fails to acknowledge the teachings of the specification and of the art

Turning to the substance of the rejection, Applicants note first that the rejection appears to incorrectly read the claim as reciting that the ligand "binds" both to pIgR and to the biologically active component. The rejection therefore fails to acknowledge the usual case, in which the ligand is covalently linked to the biologically active component, is recombinantly expressed, or complexed to the component. To improve the clarity of claim 11, a comma has been added to separate the recitation that the ligand binds to pIgR from the recitation that the construct further comprises a biologically active component. No change in the overall scope of the claim is intended.

The rejection further fails to acknowledge or to reflect the considerable amount of teaching in the specification on the production of ligands covalently linked to a therapeutic agent, see, page 53, line 30, to page 57, line 30, as well as the considerable teachings on conjugating, fusing, or complexing the biologically active molecule with the ligand. See, specification, at page 14, lines 19-25. Since the Action does not acknowledge these extensive teachings, it also contains no analysis showing that there is any reason why these teachings are insufficient to enable the person of skill in the art to make and use the ligand-biologically active agent constructs as claimed. Since the rejection fails to take into account the guidance and direction provided to the artisan, it fails to present a *prima facie* case of lack of enablement.

Applicants further observe that, in addition to chemically conjugating the binding component to the biologically active agent or expressing them as a single fusion protein where both the binding component and the biologically active component are proteins, there are numerous other methods known in the art for producing a construct of a ligand that binds to a region of pIgR and to a biologically active component. As just one example, antibodies with dual specificity can be used. Such antibodies were well known in the art before the priority date of the present specification, as shown by the fact they are the subject of a number of patents which issued prior to the priority date of the present application. Applicants respectfully call the Examiner's attention, for example, to U.S. Patent No. 5,635,600 (issued June 3, 1997) which

teaches the construction of bifunctional antibodies with binding regions derived from two separate antibodies, as well as to U.S. Patent No. 5,959,084 (issued September 28, 1999), and U.S. Patent No. 5,932,448 (issued August 3, 1999), which both likewise teach the making of bispecific antibodies.[1] (Applicants note that patents are conclusive evidence that the subject matter of their claims was considered enabled by the Patent Office as of the date of issue, and must be accepted as enabled in this proceeding.)

It would be immediately apparent that such bifunctional antibodies could be used to couple a ligand to the biologically active component. The Action concedes that the specification is enabling for an antibody that binds to the B region of pIgR. It is generally accepted in the art that antibodies can generally be generated against any antigen of interest so long as it is sufficiently immunogenic (and even relatively non-immunogenic antigens can raise antibodies if art-known methods such as adjuvants are applied). Presumably, the Action would therefore likewise concede that an antibody could also be generated against any particular biologically active component so long as it is sufficiently immunogenic. Since binding regions from two different antibodies can be used to construct bifunctional antibodies, as shown by the '600 patent, the Action has shown no reason why an appropriately designed antibody cannot bind to both the pIgR B region and to any particular biologically active component of interest.

Accordingly, Applicants respectfully submit that the rejection fails to show that claims 11-15 are not enabled for their full scope. Applicants respectfully request that the rejection be reconsidered in light of the above remarks and, upon reconsideration, be withdrawn.

(4) Rejection of the claims as not enabling production of any ligand that binds to the B region

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[1] These teachings predate the present application and therefore did not have to be explicitly taught in the specification. As the MPEP instructs, at § 2164.05(b): "The specification need not disclose what is well known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991)" (Emphasis added).

The rejection under §112, first paragraph, also rejects claims 1-4, 10-13, and 15 under §112, as not enabled for "*any* ligand comprising a binding component for binding to *any* region of [pIgR] and *any* biologically active component." Action at, e.g., page 4, top two lines (emphasis in original). In relevant part, the Action contends that Applicants have not provided "sufficient biochemical information (e.g., structural characteristics, amino acid composition, physiochemical properties, etc) that distinctly identifies such 'ligands' and 'any biological[lly] active components' other than antibodies that bind[] specifically to [the B region] and [the wildtype CFTR]." Action, at page 4. Applicants amend in part and traverse.

(a) The specification enabled the production of peptides that bind to any desired portion of pIgR

The Action asserts that the claims do not enable the production of any ligand to any portion of pIgR. As noted in preceding sections, the rejection does not take into account the recitations present in the claims under examination and does not take into account the guidance available to the practitioner. Applicants also observe that the rejection has been refuted experimentally, following art-recognized techniques available before the priority date of the present specification.

In her Declaration, Dr. Glynn states that Arizeke Pharmaceuticals, Inc. ("Arizeke"), a company developing therapeutics delivered by reverse transcytosis of pIgR, entered into a relationship with Dyax, Inc. to have Dyax's large and diverse peptide libraries screened for peptides that bind to portions of pIgR. The peptides were screened against a fusion protein of glutathione-S-transferase ("GST") fused to a peptide containing all of domain 6 and the carboxyl half of domain 5 of pIgR (the "Domain6/5 fusion protein"; the portions of pIgR within each domain are noted in Figure 1 of the specification by arrows above the sequences.) Declaration, at ¶6 and 7. Thus, the D6/D5 fusion protein encompassed both the site of the initial proteolytic cleavage of SC from the stalk, and the B region. For Arizeke's purpose of delivering therapeutics to patients, it chose to look for peptides that could bind to anywhere in this D6/D5 fusion. Persons of skill would recognize, however, that one could readily perform the same screening on a peptide consisting of the B region alone. *Id.* (Applicants also note that the use of

GST-pIgR fusion proteins to identify ligands to regions of pIgR, and methods of removing ligands reactive with GST are discussed in the specification at Example 14, page 81, line 18, to page 82, line 19.)

The peptide libraries were screened using standard phage display techniques. Phage display techniques for identifying suitable peptide ligands are discussed in the specification at, for example, page 40, lines 10-24. Phage were generated which expressed on the phage surface peptides from the library. Phage and peptides which did not bind the immobilized D6/D5fusion protein were washed away. After several rounds of screening, the peptides that best bound to the pIgR portion of the molecule were selected for further screening. The peptides identified in step 1 were then screened against MDCK cells transfected with either human, rat, or monkey pIgR. Declaration, at ¶¶8 and 9.

A total of 10 peptides were identified that not only bound to the D6/D5 portion of pIgR, but that were also internalized into the MDCK pIgR-expressing cells. Eight additional peptides were identified that bound to the cell surface. Twenty one additional peptides were identified as potential "hits" as binding to pIgR, but were not further evaluated. A total of 72 peptides were identified by their motif identity to sequences that bound to the fusion protein. Thus, dozens of peptides that bind or that are capable of binding the D6/D5 region of pIgR were identified. Declaration, at ¶10.

Accordingly, following art recognized techniques available prior to the priority date, practitioners have in fact been enabled by the specification to generate scores of peptides that bind to the D6/D5 region of pIgR. Applicants respectfully maintain that the claims are enabled for their full scope.

(b) Application of the *Wands* factors

As part of the rejection of the claims as not enabled, the Action asserts that undue experimentation would be required to practice the claims for their full scope. In this regard, the Action states that undue experimentation would be needed to practice the invention. Action, at page 4.

As shown above, the rejection is based in part on an overbroad reading of the claims. The rejection fails, for example, to note the recitations concerning the portion of the pIgR molecule to which the ligands are stated to bind.

Applicants further maintain that the undue experimentation is not needed to practice the claims under examination. The Action appears to assume that if any experimentation is required, that constitutes "undue" experimentation. In fact, however, an invention can require considerable experimentation to practice so long as that experimentation is not "undue." As the Action correctly notes, whether or not experimentation is "undue" is determined under criteria that were articulated by the Federal Circuit in *In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Those criteria are: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

While the Action acknowledges the *Wands* factors, it provides only a summary of the factors, without a careful analysis of why the claims are allegedly not enabled in light of the present specification and the knowledge in the art. Application of the *Wands* criteria to the present claims shows that persons of skill in the art were fully enabled to use the invention as claimed without undue experimentation:

Factor 1: The breadth of the claims. The claims are narrowly drawn to ligands that bind to a defined region (the "B region") of a defined, known molecule, the polymeric immunoglobulin receptor. This factor therefore argues that the claims are enabled.

Factor 2: The nature of the invention. The invention is related to the surprising realization that the B region provides a target that permits internalization of a higher percentage of targeted biologically active components than is true for components targeted to the major species of the secretory component present in a target organ. This factor is neutral.

Factor 3: The state of the prior art. The prior art sets forth teachings regarding targeting antibodies to the distal portion of the secretory component (Ferkol) and to the stalk (co-owned U.S. Patent No. 6,042,833). Further, the art teaches methods, such as phage display, for

rapidly screening large libraries of peptides that can bind to any particular target of interest, such as the B region of pIgR. *See*, Declaration of Dr. Jacqueline M. Glynn. Thus, this factor cuts in favor of enablement of the present invention.

Factor 4: The level of skill in the art. Persons of skill in this art are typically medical doctors and Ph.D. level specialists. Therefore, the level of skill in the art is very high indeed, and the amount of guidance that they need to be provided is correspondingly limited. This factor, too, cuts in favor of enablement.

Factor 5: The predictability in the art. The Action does not assert that there is unpredictability regarding antibodies that can bind to the B region. The Action does appear to assert that finding peptides that would to the B region is unpredictable. Applicants respectfully note that, while it may be unpredictable whether any particular peptide will bind to the B region, it is predictable that screening large libraries of peptides will likely result in identifying some peptides that do bind. *See*, *generally*, Declaration of Dr. Jacqueline M. Glynn. Applicants respectfully maintain that it is not unpredictable that peptides that bind the B region can be identified using art recognized techniques. Thus, while the individual peptides may themselves be patentable, so are the present claims. Thus, Applicants maintain that this factor as well weighs in favor of finding that any experimentation required is not undue.

Factor 6: The amount of direction provided. The specification provides ample guidance as to how to make and use the invention as claimed. As already noted, the Action fails to acknowledge or to consider, the direction provided in the specification. For example, the specification provides both detailed guidance on generating antibodies (see, page 38, line 5, to page 40, line 9) and a discussion on using phage display techniques for identifying suitable peptide ligands specification at page 40, lines 10-24. The specification further sets forth methods for determining whether any particular peptide binds to the B region (see, page 44, line 8, to page 46, line 6), and detailed assays for making those determinations (e.g., Example 9, page 74, line 30, to page 76, line 14). The Examples further set forth an Example on testing the binding of protein ligands in filamentous phage (see, Example 12, page 77, line 31, to page 78, line 17; it should be noted that antibodies are proteins), as well as an example describing the use of GST-fusion proteins for screening ligands. (See, Example 14, page 81, line 17, to page 82, line 19).

As noted in regard to Factor 4, persons in this art are highly skilled and need correspondingly lower levels of guidance to practice the invention. Accordingly, this factor as well weighs in favor of finding that any experimentation required is not undue.

Factor 7: The number of working examples. The Action summarily dismisses "the limited working examples." Action at page 4. Applicants respectfully note that the specification provides fourteen examples, which set forth, among other things, a very detailed assays for demonstrating that a ligand binds to the B region (Example 7, page 66, line 26, to page 72, line 25), an exemplary protocol for *in vivo* testing of ligand binding (Example 9, page 74, line 30, to page 76, line 14) and a detailed assay for determining the epitopes to which scFv expressed in filamentous phage bound (Example 12, page 77, line 31, to page 78, line 17). The Action fails to acknowledge the presence of these detailed teachings, or why the guidance provided is not sufficient to show the person of skill in this art - who are, after all, Ph.D.s and M.D.s -- how to practice the invention.

Factor 8: The quantity of experimentation needed to make or use the invention based on the content of the disclosure. Persons of skill can generate antibodies against any particular antigen of interest. See, specification at page 37, line 7 to page 40, line 9. The specification further describes phage display, an art-recognized technique, for rapidly screening large libraries of peptides for peptides that bind to any particular target, such as the B region. See, specification at page 40, lines 10-24. Moreover, following precisely this technique, peptides have been identified that bind to stretches of pIgR that include the B region. See, Glynn Declaration, at ¶ 10. Accordingly, the predictions set forth in the specification have thus far been borne out in practice.

Applicants maintain that application of the *Wands* factors to the present claims supports finding that undue experimentation is not required to practice the invention.

D. Rejection of the Claims as Allegedly Not in the Possession of the Invention

Claims 1-4, 10-13, and 15 are rejected under 35 U.S.C. § 112, first paragraph as containing subject matter which was not described in such a way as to reasonably convey that the

inventors had possession of the invention at the time the application was filed. Action, at page 5. In language closely resembling that of the enablement rejection, the Action states that the specification does not show

> that there is any per se structure/function relationship between the disclosed antibody that binds specifically to a B region of pIgR . . . and *any* ligand that binds to any region of pIgR or any ligand comprising a binding component for binding to *any* region of [pIgR] and *any* biologically active component.

Action, at page 5. According to the Action, a genus of ligands may be achieved only by means of reciting a representative number of ligands defined by amino acid sequence or a recitation of structural features common to the genus. The Action further alleges that the specification does not allow persons of ordinary skill to recognize that the inventors what is claimed. Action, at page 6. Applicants amend in part and traverse.

The rejection is founded on a false premise. As previously observed with respect to the enablement rejection, the claims under examination do not recite or require ligands that bind "*any* region of pIgR". Claim 1 begins by reciting "[a] ligand that binds specifically to a region of a polymeric immunoglobulin receptor," it continues by reciting that the ligand "does not substantially bind to the most abundant form of [secretory component] present in the organ of interest and provided further that the ligand does not bind substantially to the stalk." Thus, claim 1 does not recite ligands that bind to *any* portion of pIgR, as the Action asserts, but rather ligands that bind to a region of pIgR positioned between the most abundant form of the SC and the stalk -- what the specification terms the "B region."

Thus, the rejection is based in part on ignoring two functional recitations regarding where the ligands of the invention bind, which define the ligands as binding to the B region. Since the other claims under examination depend from claim 1 and, therefore share the same recitations, they too refer to ligands that bind the B region. Accordingly, the written description rejection of claims 1-4, 10-13, and 15 is founded on an erroneous reading of those claims, and should be reconsidered, and withdrawn on this basis alone.

The rejection is based on further misreading of the claims to contend that the ligand binds to any biologically active component. As with the enablement rejection, Applicants

note that this portion of the rejection can apply only to claims 11-15, since they are the only claims under examination that contain a recitation that the ligand further comprises a binding component and a biologically active component. Thus, this portion of the written description rejection is not applicable to claims 1-4 or 10.

Turning to the substance of the rejection, once again Applicants note that the rejection appears to incorrectly read the claim as reciting that the ligand "binds" both to pIgR and to the biologically active component. The rejection therefore fails to acknowledge the usual case, in which the ligand is covalently linked to the biologically active component, is recombinantly expressed, or complexed to the component. As noted with respect to the enablement rejection, to improve the clarity of claim 11, a comma has been added to separate the recitation that the ligand binds to pIgR from the recitation that the construct further comprises a biologically active component. No change in the overall scope of the claim is intended.

The rejection further fails to acknowledge or to reflect the considerable amount of teaching in the specification on the production of ligands covalently linked to a therapeutic agent, see, page 53, line 30, to page 57, line 30, as well as the considerable teachings on conjugating, fusing, or complexing the biologically active molecule with the ligand. See, specification, at page 14, lines 19-25. Since the Action does not acknowledge these extensive teachings, it also contains no analysis showing that there is any reason why these teachings do not provide an adequate description of the ligand-biologically active agent constructs claimed. For this reason, too, the written description rejection should be reconsidered, and withdrawn.

Applicants further note that claim 1 has been amended to recite antibody or peptide ligands. Applicants respectfully remind the Examiner that MPEP §2163 requires that, before repeating the written description requirement in any future action, the Examiner is required to reconsider the rejection in light of this reply. Applicants further remind the Examiner that, pursuant to MPEP §2163.04: "A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. . . . [citation to *Marzocchi* omitted]. The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would

not recognize in an applicant's disclosure a description of the invention defined by the claims." Applicants respectfully maintain that a person of skill would recognize in Applicants' present disclosure a description of the invention defined by the claims as presented.

E. Rejections of the Claims as Anticipated

Claims 1-7 and 10 are rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 6,046,037 (the "'037 patent"), by Bost et al., Immunol Invest 17:577-586 (1988) ("Bost"), and Bendayan, J. Histochem Cytochem 43:881-886 (1995) ("Bendayan"). Applicants traverse.

According to the Action, the '037 patent teaches an antibody that can bind to amino acids 450-606 of an animal pIgR, and that the region of this pIgR is highly homologous to the pIgR sequence discussed in the present specification. Moreover, the Action asserts that the '037 patent teaches that the antibody is a humanized antibody or consists of a recombinant single variable region. Action at page 6, item 11.

Applicants respectfully observe that this rejection is based on a straightforward misreading of the '037 patent. The '037 concerns the production of immunoglobulins in transgenic plants. The patent further teaches "protection proteins", which are fragments of pIgR, and which are capable of binding to certain immunoglobulins, especially polymeric IgA and IgM, to permit the production of recombinant secretory immunoglobulins. As the inventors of the '037 patent note, at column 3, lines 36-39, "we have assembled secretory immunoglobulin composed of alpha, J, and kappa immunoglobulin chains associated with a protection protein derived from pIgR. This invention provides transgenic plants that assemble secretory immunoglobulins with great efficiency." (Emphasis added.)

Thus, the '037 does not teach the production of antibodies to portions of pIgR, as the rejection asserts, but rather the production of antibodies comprising portions of pIgR. Applicants surmise the Action may have mistaken the use of antibodies to detect the recombinant constructs reported at column 39, line 64, to column 40, line 53 to involve the use of antibodies

directed to pIgR.[2] The cited section concerns the use of ELISA assays comprising goat antibodies to the mouse heavy and light chain to detect the presence of these chains in the recombinant constructs produced by the plants. The antibodies used in the ELISAs, however, are to the immunoglobulin chains, not to the pIgR protection protein. Accordingly, the '037 patent does not teach ligands which bind any portion of pIgR, let alone ligands which bind the B region.

Bost and Bendayan are included in the rejection to provide support for the proposition that the antibodies to pIgR allegedly taught in the '037 patent would cross-react with portions of the B region, which the Action indicates are highly homologous with the portion of pIgR taught in the '037 patent. As shown above, however, the Action's assumption that the '037 patent teaches antibodies binding to pIgR is based on a misreading of the patent. The '037 patent does not teach such antibodies and the teachings of Bost and Bendayan are therefore irrelevant to the consideration of the claims under examination.

To the extent that the Action is based on reading the '037 to teach ligands that bind to pIgR, it is based on a misreading of the patent. The rejection should be reconsidered and, upon reconsideration, should be withdrawn.

F. Rejection of the Claims as Obvious

Claims 1, 11, 12, 13, and 15 are rejected under 35 U.S.C. § 103(a) as obvious over the '037 patent, Bost, and Bendayan, in view of U.S. Patent No. 6,440,419 (the '419 patent) and U.S. Patent No. 6,340,743 (the "'743" patent). The Action relies on the alleged teachings of the '037 patent, Bost and Bendayan, but concedes that they do not teach an antibody comprising a binding component to pIgR and a biologically active component, where the biologically active component is a wildtype cystic fibrosis transmembrane regulator ("CFTR") or a small molecule. Action, at page 8, item 13. The Action states, however, that the '419 patent teaches antibodies for the delivery of biologically active components, including therapeutic agents and small

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[2] Applicants assume that the Action's references to "pages" 38 and 39 of the '037 patent refer to the columns bearing those numbers, since pages 38 and 39 of the printed patent are part of the sequence listing.

molecules. *Id.* The Action cites the '743 patent for teaching an antibody to the pIgR stalk comprising a wildtype CFTR. *Id.* The Action concludes that it would have been obvious to combine the teachings of the '419 and '743 patents with those of the '037 patent to obtain an antibody to pIgR and a wildtype CFTR. Action, at page 9. Applicants traverse.

The rejection is founded on the presumption that the '037 patent teaches antibodies that bind to a portion of pIgR. As shown in the preceding section, the '037 patent does not teach antibodies to any portion of pIgR, but rather the recombinant production in plants of immunoglobulins associated with pIgR. Thus, as shown in the preceding section, there are no antibodies to pIgR to combine with the teachings of Bost and Bendayan to come up with the ligands claimed in the claims under examination.

The deficiencies of the '037 patent are not made up by the '419 patent. The '419 patent is cited because it teaches use of a targeting molecule to epithelial cells to deliver biologically active molecules. Since it does not teach or suggest antibodies to pIgR, however, it cannot render obvious the claimed ligands to the B region of pIgR, alone or in combination with the other references.

The deficiencies of the '037 patent are likewise not made up by the '743 patent, which issued to two of the inventors of the present invention. The '743 patent is cited because it teaches the delivery of CFTR to cells using an anti-pIgR antibody. But, it cannot render obvious the use of the ligands of the claims under examination since the '743 patent does not teach or suggest the advantages of using ligands targeted to the B region of pIgR, alone or in combination with the other references.

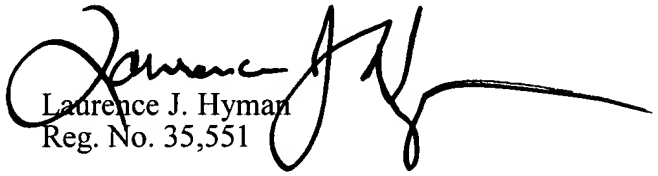
As with the anticipation rejection, the obviousness rejection is grounded on a misreading of the '037 patent. Properly read, the '037 patent does not teach antibodies to pIgR, and therefore has no teachings relevant to the present claims to combine with the teachings of the other references. The rejection should be reconsidered and, upon reconsideration, should be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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Attachment: Declaration of Dr. Glynn

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